

70. An isolated nucleic acid molecule consisting of a nucleotide sequence as set forth in any one of SEQ ID NO: 3, SEQ ID NO: 9 or SEQ ID NO: 11, or a nucleotide sequence which hybridizes under low stringency conditions to any one of SEQ ID NO: 3, SEQ ID NO: 9 or SEQ ID NO: 11, wherein said low stringency conditions comprise at least about 1% v/v to at least about 15% v/v formamide at least about 1M to about 2M salt for hybridization at 42 °C, and at least about 1M to about 2M salt for washing, and wherein said nucleotide sequence encodes a protein which suppresses cytokine-mediated signaling.

#### REMARKS

In the Office Action dated April 19, 2002, claims 6-12 and 41-67 are pending. The Examiner has made the Restriction Requirement final. Consequently, claims 6-12 and 41-67 are examined to the extent that these claims pertain to the elected SOCS1 nucleic acid molecules, the encoded SOCS1 proteins and related vectors and host cells. Claims 6-12 and 41-60 are rejected under 35 U.S.C. §102(a) as allegedly anticipated by Schluter et al. (January 1996). Claims 6-12, 41-45, 47, 48 and 50-67 are rejected under the written description requirement of 35 U.S.C. §112, first paragraph. Claims 6-12 and 41-67 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 62-67 are rejected under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 1-12 of U.S. Patent 6,323,317, issued from the related application Serial No. 09/302,769. Claims 63-67 are further rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-10 and 13-15 of the '317 patent. In addition, the specification is objected to for certain informalities.

This Response addresses each of the Examiner's rejections and objections.

Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

With respect to the specification, the Examiner has pointed out that sequence identifiers have not been placed throughout the specification, e.g., at page 6, line 9. The Examiner also states that all amino acids should be written using the three-letter code as required under 37 C.F.R. 1.821. In addition, the Examiner states that the specification improperly incorporates sequences, e.g., at page 76.

In response, Applicants have provided herewith substitute, amended page 6, 7, 9, 12, 14, 33, 39 and 41, in which the sequence identifier for SEQ ID NO: 51 has been inserted.

As to amino acids, a number of places of the specification reference amino acids by their one-letter codes. There is no ambiguity as to the purpose and meaning of these one-letter codes – that is, one skilled in the art clearly understands that they represent amino acids in light of the specification. In addition, Applicants have submitted a formal Sequence Listing where all the amino acids are written by their three-letter codes, as required under 37 C.F.R. §1.821. It is not necessary for Applicants to also use the three-letter code for amino acids in the specification.

With respect to the alleged improper incorporation of sequences, it is observed that the specification references a number of sequences by their Genbank identification/accession numbers. The Examiner has not explained as to why such references are inappropriate.

Applicants respectfully submit that given an accession number, those skilled in the art can obtain the corresponding sequence from the Genbank database, which is accessible by the public.

In view of the foregoing, it is respectfully submitted that the objection to the specification is obviated. Withdrawal of the objection to the specification is therefore respectfully requested.

Turning to the claims, the Examiner has made the Restriction Requirement final. Consequently, claims 6-12 and 41-67 are examined to the extent that these claims pertain to the elected SOCS1 nucleic acid molecules, the encoded SOCS1 proteins and related vectors and host cells. The Examiner has requested Applicants to amend the claims to reflect the election.

In response, Applicants have canceled claims 6-12 and 41-51 without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in one or more continuing applications.

Applicants have also added claims 68-70, drawn to nucleic acid molecules consisting of a nucleotide sequence which encodes a protein that suppresses cytokine-mediated signaling. Support for these new claims is found throughout the specification and in original claims 52-54. No new matter is introduced.

Claims 62-67 are rejected under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 1-12 of U.S. Patent 6,323,317, issued from the related application Serial No. 09/302,769.

Applicants respectfully disagree with the Examiner in this regard. It is observed that claims 1-12 of the '317 patent are directed to isolated proteins of the SOCS family, characterized by a SOCS box motif:  $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}[X_i]_nX_{17}X_{18}X_{19}X_{20}X_{21}X_{22}X_{23}[X_j]_nX_{24}X_{25}X_{26}X_{27}X_{28}$  (see claims 1-2 of the '317 patent). Claims 3-4 of the '317 patent further delineate the SOCS box motif as selected from SEQ ID NOS: 64-81 or a sequence having at least about 70% similarity to any one of SEQ ID NOS: 64-81. SEQ ID NOS: 64-81 represent the SOCS box

sequences of various SOCS proteins from human, murine and rat, where SEQ ID NOS: 64 and 67 represent the SOCS box motif of the murine SOCS1 and human SOCS1 proteins. Claim 11 of the '317 patent further defines the protein as comprising an amino acid sequence as set forth in any one of SEQ ID NOS: 4, 6, 8, 10, 12, 14, 18, 21, 25, 29, 36, 41, 44, 46, 48, 57, 61 or 63, or an amino acid sequence having at least 50% similarity to any of these sequences, wherein SEQ ID NOS: 4, 10 and 12 represent the SOCS1 protein sequences from murine, human and rat, respectively. Claim 12 of the '317 patent defines the protein by its encoding nucleotide sequence. In contrast to an isolated protein of the SOCS family as claimed in the '317 patent, claims 62-67 of the present application is directed to an isolated SOCS1 protein or a protein sharing similarity to a SOCS1 protein.

Applicants respectfully submit that a statutory double patenting is proper only if the present application claims the same invention of the issued patent. One of the tests for determining whether the two sets of claims are directed to identical subject matter is to assess whether there is an embodiment that falls within one set of claims, but not the other set. See MPEP 804, IIA (page 800-20). If there is such an embodiment, then the two sets of claims do not define identical subject matter and double patenting would not exist. In the instant case, there could be an isolated protein of the SOCS family that shares 50% similarity to some other members of the SOCS family but not SOCS1, or that has a SOCS box motif that shares 70% similarity to the SOCS box motifs of some other members of the SOCS family but not the SOCS box motif of SOCS1. Therefore, it is respectfully submitted that instant claims 62-67 do not claim identical subject matter as claims 1-12 of the '317 patent.

In view of the foregoing, the statutory double patenting rejection of claims 62-67 under 35 U.S.C. §101 is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 63-67 are further rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-10 and 13-15 of the '317 patent.

Applicants acknowledge that this obviousness-type double patenting rejection can be overcome by timely filing a terminal disclaimer to disclaim the term of the patent issuing from the present application that is in excess of the term of the '317 patent.

Claims 6-12, 41-45, 47, 48 and 50-67 are rejected under the written description requirement of 35 U.S.C. §112, first paragraph.

The Examiner observes that claims 6 and 41 are drawn to nucleic acid molecules encoding a protein comprising a SOCS box. The Examiner contends that the specification has not set forth the function of the SOCS box. While acknowledging that claim 42 sets forth specific sequences of the SOCS box, the Examiner argues that the SOCS box is only a part of the entire protein and that the function of the full-length protein recited in the claims is not set forth. The Examiner has suggested that Applicants include a specific function of the claimed molecule in the claims, e.g., "wherein said protein inhibits IL-6-mediated signal transduction."

Applicants will address the rejection insofar as it concerns claims 52-67, as claims 6-12 and 41-51 have been canceled without prejudice. Claims 52-67 are drawn to isolated nucleic acid molecules, the encoded proteins, the vectors and host cells, where the isolated nucleic acid molecules are identical or hybridize to specified SOCS1 nucleotide sequences, or encode a protein which is identical or shares sequence similarity to specified SOCS1 proteins, or encode a

protein having a SOCS box motif that is identical or shares sequence similarity to the SOCS boxes of the specified SOCS1 proteins.

By way of the instant amendment, claims 52-67 have been amended to add the functional language “wherein said protein suppresses cytokine-mediated signaling.” Applicants respectfully submit that the specification provides at least three species of SOCS1 molecules, i.e., the SOCS1 molecules isolated from human, murine and rat. In view of the amendment to the claims and the description in the specification, Applicants respectfully submit that the isolated nucleic acid molecules and proteins, as presently claimed, are adequately characterized by both structure (sequence) and function. Therefore, the written description requirement under 35 U.S.C. §112, first paragraph, is full satisfied.

Accordingly, the rejection of the claims under the written description requirement under 35 U.S.C. §112, first paragraph, is obviated. Withdrawal of the rejection is therefore respectfully requested.

Claims 6-12 and 41-67 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite.

The Examiner states that the claims have not been amended to reflect the elected invention of SOCS1 molecules. It is respectfully submitted that Applicants have canceled claims 6-12 and 41-51 without prejudice in favor of claims 52-67, drawn to the elected embodiments.

The Examiner further states that acronyms are used throughout the claims, which render the claims indefinite. Applicants have amended claims 58 and 67 to replace the term “IL-6” with the full name “Interleukin-6”.

Furthermore, the Examiner contends that the term “modulates signal transduction” in claims 7-9, 56-58 and 65-67 renders the claims indefinite. It is respectfully submitted that claims

7-9, 57-58 and 65-66 have been canceled without prejudice. The objected term has also been deleted from claims 58 and 67.

Moreover, the Examiner contends that claim 53 is not clear as to whether the protein, which shares 50% similarity to SEQ ID NO: 4, e.g., must also include a SOCS box having at least 70% similarity to SEQ ID NO: 52 or 55.

Applicants respectfully submit that claim 52 characterizes the protein as comprising a SOCS box, which box is set forth in SEQ ID NO: 52 or 55, or has at least 70% similarity to SEQ ID NO: 52 or 55. As claim 53 depends from claim 52 and refers to “said protein” in claim 52, such protein in claim 53 have all the delineations of the protein in claim 52. Nevertheless, Applicants have amended claim 53 to clarify that said protein is “further characterized as...”. Claim 53, as presently amended, is not indefinite.

In addition, the Examiner points out that the term “said protein” as used in claims 56-60 lacks antecedent basis, because claim 56 depends from claim 54 and claim 54 does not mention any protein. It is respectfully submitted that claim 54 has been amended to recite that the nucleic acid molecule “encodes a protein which suppresses cytokine-mediated signaling,” thereby providing an antecedent basis for the term “said protein” as recited in claims 56-60.

In view of the foregoing, it is respectfully submitted that the rejection of the claims under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 6-12 and 41-60 are rejected under 35 U.S.C. §102(a) as allegedly anticipated by Schluter et al. (*Molecular Reproductive Development* 43: 1-6, 1996).

According to the Examiner, Schluter et al. teach a nucleic acid sequence of Z47352 which has 98.6% identity to instant SEQ ID NO: 3 (murine SOCS1); a nucleic acid sequence of

Z46940 which has 99.3% identity to instant SEQ ID NO: 9 (human SOCS1); and a nucleic acid sequence of Z46939 which has 100% identity to instant SEQ ID NO: 11 (rat SOCS1).

From the partial Genbank sequence reports provided by the Examiner, Applicants observe that the nucleic acid molecules having the accession number Z47352, Z46940 and Z46939 are large molecules of 13812bp, 28535bp and 13187bp in length (“bp” for “base pair”), respectively. On the other hand, the instant SOCS1 nucleotide sequences are only 1235 (murine), 1094 (human) and 2087 bp (rat), respectively. The sequence alignment, which has been provided by the Examiner, shows that instant SEQ ID NO: 3 (murine SOCS1, 1235 bp) has 98.6% identity to a 1226bp portion of the nucleic acid molecule Z47352; that instant SEQ ID NO: 9 (human SOCS1, 1094bp) has 99.3% identity to a 1089bp portion of the nucleic acid molecule Z46940; and that instant SEQ ID NO: 11 (rat SOCS1, 2807bp) bears 100% identity to a 2807bp portion of the nucleic acid molecule Z46939.

Applicants observe that the Schluter article was published in the journal of *Molecular Reproductive Development* in January, 1996. The article teaches the isolation of a number of nucleic acid molecules. However, there is no indication anywhere in the article that these nucleic acid molecules were made available to the public, e.g., by way of deposit with a public depository. Furthermore, the article does not disclose the sequence of any of these molecules. The authors claim that the sequences of these molecules have been submitted to GenBank and have been assigned with accession numbers, including accession numbers Z47352, Z46940 and Z46939. However, there is no indication in the Schluter article that these sequences were published or made available to the public as of January, 1996. The partial Genbank reports provided by the Examiner seem to indicate that the sequences of Z47352, Z46940 and Z46939 were published on December 11, 1996, May 24, 2000, and December 11, 1996, respectively, all

after the priority date of November 1, 1996 of the present application. See the first line in the partial sequence reports provided by the Examiner for Z47352, Z46940 and Z46939, respectively.

Applicants have also obtained the complete sequence reports from the Genbank NCBI database for Z47352, Z46940 and Z46939, copies of which are enclosed hereto as **Exhibits A-C**. The reports indicate that Schluter et al. made several submissions to Genbank for each of the sequences designated as Z47352, Z46940 and Z46939. There is no information in the reports as to the extent and content of the earlier submissions. It seems that the earlier versions of the sequences designated as Z47352, Z46940 and Z46939, respectively were replaced with the final versions of the sequences on June 5, 1996, June 3, 2000, and June 5, 1996, respectively. As to Z47352 and Z46939, there is no information that the final versions were "published" by Genbank prior to November 1, 1996, the priority date of the present application. As to Z46940, the final version was clearly made available to the public after the priority date of the present application.

In view of the foregoing, Applicants respectfully submit that Schluter et al. did not publicly disclose the isolated nucleic acid molecules having accession numbers of Z47352, Z46940 and Z46939, respectively, prior to the priority date of the present application of November 1, 1996. Therefore, Schluter et al. is not a proper prior art reference under §102(a). Thus, the rejection of the claims under 35 U.S.C. 102(a) based on Schluter is overcome. Withdrawal of the rejection is therefore respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the instant amendment. The attached page is captioned "Version with Markings to Show Changes Made."

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

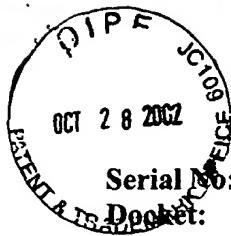
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

**Please amend pages 6, 7, 9, 12, 14, 33, 39 and 41 as indicated in the attached marked-up copies of these pages.**

**IN THE CLAIMS:**

**Please cancel claims 6-12, 41-51 and 56-57 without prejudice.**

**Please amend the remaining claims as follows:**

52. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence which encodes [encoding] a protein, wherein said protein [which] comprises a SOCS box [, wherein said SOCS box] which comprises an amino acid sequence as set forth in SEQ ID NO: 52 or SEQ ID NO: 55, or an amino acid sequence having at least about 70% similarity to SEQ ID NO: 52 or SEQ ID NO: 55, and wherein said protein suppresses cytokine-mediated signaling.

53. (Amended) The isolated nucleic acid molecule of claim 52, wherein said protein is further characterized as comprising [comprises] an amino acid sequence as set forth in any one of SEQ ID NO: 4, SEQ ID NO: 10 or SEQ ID NO: 12, or an amino acid sequence having at least about 50% similarity to any one of SEQ ID NO: 4, SEQ ID NO: 10 or SEQ ID NO: 12.

54. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in any one of SEQ ID NO: 3, SEQ ID NO: 9 or SEQ ID NO: 11, or a nucleotide sequence which hybridizes under low stringency conditions to any one of SEQ ID NO: 3, SEQ ID NO: 9 or SEQ ID NO: 11, wherein said low stringency conditions comprise at least about 1% v/v to at least about 15% v/v formamide at least about 1M to about 2M salt for hybridization at

42°C, and at least about 1M to about 2M salt for washing, and wherein said nucleotide sequence encodes a protein which suppresses cytokine-mediated signaling.

55. (Amended) The isolated nucleic acid molecule of any one of claims 52-54 or 68-70, wherein said nucleic acid molecule is derived from mouse, rat or human.

58. (Amended) The isolated nucleic acid molecule according to [claim 57] any one of claims 52-54 or 68-70, wherein [the signal transduction is mediated by IL-6 ] said cytokine is Interleukin-6.

59. (Amended) An expression vector comprising the nucleic acid molecule of any one of claims 52-54 or 68-70.

62. (Twice Amended) An isolated protein comprising a SOCS box, wherein said SOCS box comprises an amino acid sequence as set forth in SEQ ID NO: 52 or SEQ ID NO: 55, or an amino acid sequence having at least about 70% similarity to SEQ ID NO: 52 or SEQ ID NO: 55, and wherein said protein suppresses cytokine-mediated signaling.

63. (Twice Amended) An isolated protein comprising an amino acid sequence as set forth in any one of SEQ ID NO: 4, SEQ ID NO: 10 or SEQ ID NO: 12, or an amino acid sequence having at least about 50% similarity to any one of SEQ ID NO: 4, SEQ ID NO: 10 or SEQ ID NO: 12, and wherein said protein suppresses cytokine-mediated signaling.

67. (Amended) The isolated protein [of claim 66] according to claim 62 or 63, wherein [the signal transduction is mediated by IL-6] said cytokine is Interleukin-6.

**Please add the following claims:**

68. An isolated nucleic acid molecule consisting of a nucleotide sequence which encodes a protein, wherein said protein comprises a SOCS box which comprises an amino acid sequence as set forth in SEQ ID NO: 52 or SEQ ID NO: 55, or an amino acid sequence having at

least about 70% similarity to SEQ ID NO: 52 or SEQ ID NO: 55, and wherein said protein suppresses cytokine-mediated signaling.

69. The isolated nucleic acid molecule of claim 68, wherein said protein is further characterized as comprising an amino acid sequence as set forth in any one of SEQ ID NO: 4, SEQ ID NO: 10 or SEQ ID NO: 12, or an amino acid sequence having at least about 50% similarity to any one of SEQ ID NO: 4, SEQ ID NO: 10 or SEQ ID NO: 12.

70. An isolated nucleic acid molecule consisting of a nucleotide sequence as set forth in any one of SEQ ID NO: 3, SEQ ID NO: 9 or SEQ ID NO: 11, or a nucleotide sequence which hybridizes under low stringency conditions to any one of SEQ ID NO: 3, SEQ ID NO: 9 or SEQ ID NO: 11, wherein said low stringency conditions comprise at least about 1% v/v to at least about 15% v/v formamide at least about 1M to about 2M salt for hybridization at 42°C, and at least about 1M to about 2M salt for washing, and wherein said nucleotide sequence encodes a protein which suppresses cytokine-mediated signaling.

Even still a further aspect of the present invention is directed to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a derivative, homologue, analogue or mimetic thereof or a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein 5 comprises a SOCS box in its C-terminal region wherein the SOCS box comprises the amino acid sequence:

X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> X<sub>4</sub> X<sub>5</sub> X<sub>6</sub> X<sub>7</sub> X<sub>8</sub> X<sub>9</sub> X<sub>10</sub> X<sub>11</sub> X<sub>12</sub> X<sub>13</sub> X<sub>14</sub> X<sub>15</sub> X<sub>16</sub> [X<sub>17</sub>]<sub>n</sub> X<sub>17</sub> X<sub>18</sub> X<sub>19</sub> X<sub>20</sub>  
X<sub>21</sub> X<sub>22</sub> X<sub>23</sub> [X<sub>24</sub>]<sub>n</sub> X<sub>24</sub> X<sub>25</sub> X<sub>26</sub> X<sub>27</sub> X<sub>28</sub> (SEQ ID NC:51)

10

wherein: X<sub>1</sub> is L, I, V, M, A or P;

X<sub>2</sub> is any amino acid residue;

X<sub>3</sub> is P, T or S;

X<sub>4</sub> is L, I, V, M, A or P;

15

X<sub>5</sub> is any amino acid;

X<sub>6</sub> is any amino acid;

X<sub>7</sub> is L, I, V, M, A, F, Y or W;

X<sub>8</sub> is C, T or S;

X<sub>9</sub> is R, K or H;

20

X<sub>10</sub> is any amino acid;

X<sub>11</sub> is any amino acid;

X<sub>12</sub> is L, I, V, M, A or P;

X<sub>13</sub> is any amino acid;

X<sub>14</sub> is any amino acid;

25

X<sub>15</sub> is any amino acid;

X<sub>16</sub> is L, I, V, M, A, P, G, C, T or S;

[X<sub>17</sub>]<sub>n</sub> is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X<sub>17</sub> may comprise the same or different amino acids selected from any amino acid residue;

30

X<sub>17</sub> is L, I, V, M, A or P;

X<sub>18</sub> is any amino acid;

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X<sub>19</sub> is any amino acid;X<sub>20</sub> L, I, V, M, A or P;X<sub>21</sub> is P;X<sub>22</sub> is L, I, V, M, A, P or G;5 X<sub>23</sub> is P or N;[X<sub>j</sub>]<sub>n</sub> is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X<sub>j</sub> may comprise the same or different amino acids selected from any amino acid residue;X<sub>24</sub> is L, I, V, M, A or P;10 X<sub>25</sub> is any amino acid;X<sub>26</sub> is any amino acid;X<sub>27</sub> is Y or F;X<sub>28</sub> is L, I, V, M, A or P;

15 and a protein:molecule interacting region such as but not limited to one or more of an SH2 domain, WD-40 repeats and/or ankyrin repeats N-terminal of the SOCS box.

Another aspect of the present invention is directed to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a derivative, homologue, analogue or mimetic thereof or a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein exhibits the following characteristics:

(i) comprises a SOCS box in its C-terminal region having the amino acid sequence:

25 X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> X<sub>4</sub> X<sub>5</sub> X<sub>6</sub> X, X<sub>8</sub> X<sub>9</sub> X<sub>10</sub> X<sub>11</sub> X<sub>12</sub> X<sub>13</sub> X<sub>14</sub> X<sub>15</sub> X<sub>16</sub> [X<sub>j</sub>]<sub>n</sub> X<sub>17</sub> X<sub>18</sub> X<sub>19</sub> X<sub>20</sub>  
X<sub>21</sub> X<sub>22</sub> X<sub>23</sub> [X<sub>j</sub>]<sub>n</sub> X<sub>24</sub> X<sub>25</sub> X<sub>26</sub> X<sub>27</sub> X<sub>28</sub> (SEQ ID NO: 51)

wherain: X<sub>1</sub> is L, I, V, M, A or P;

X<sub>2</sub> is any amino acid residue;

30 X<sub>3</sub> is P, T or S;

X<sub>4</sub> is L, I, V, M, A or P;

protein:molecule interacting domain in a region N-terminal of the SOCS box.

Preferably, the SOCS molecules modulate signal transduction such as from a cytokine or hormone or other endogenous or exogenous molecule, a microbe or microbial product, an antigen or a parasite.

More preferably, the SOCS molecule modulate cytokine mediated signal transduction.

Still another aspect of the present invention comprises a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a derivative, homologue, analogue or mimetic thereof or comprises a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein exhibits the following characteristics;

- (i) is capable of modulating signal transduction;
- 15 (ii) comprises a SOCS box in its C-terminal region having the amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_j]_a X_{17} X_{18} X_{19} X_{20}$   
 $X_{21} X_{22} X_{23} [X_j]_b X_{24} X_{25} X_{26} X_{27} X_{28}$  (SEQ ID NO: 51)

20       wherein:      $X_1$  is L, I, V, M, A or P;  
 $X_2$  is any amino acid residue;  
 $X_3$  is P, T or S;  
 $X_4$  is L, I, V, M, A or P;  
 $X_5$  is any amino acid;  
25        $X_6$  is any amino acid;  
 $X_7$  is L, I, V, M, A, F, Y or W;  
 $X_8$  is C, T or S;  
 $X_9$  is R, K or H;  
 $X_{10}$  is any amino acid;  
30        $X_{11}$  is any amino acid;  
 $X_{12}$  is L, I, V, M, A or P;

Another aspect of the present invention contemplates a protein or a derivative, homologue, analogue or mimetic thereof comprising a SOCS box in its C-terminal region and a SH2 domain, WD-40 repeats or ankyrin repeats N-terminal of the SOCS box.

5 Still yet another aspect of the present invention provides a protein or a derivative, homologue, analogue or mimetic thereof exhibiting the following characteristics:

(i) comprises a SOCS box in its C-terminal region having the amino acid sequence:

10  $X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_i]_n X_{17} X_{18} X_{19} X_{20}$   
 $X_{21} X_{22} X_{23} [X_j]_n X_{24} X_{25} X_{26} X_{27} X_{28}$  (SEQ ID N°: 51)

wherein:  $X_1$  is L, I, V, M, A or P;

$X_2$  is any amino acid residue;

15  $X_3$  is P, T or S;

$X_4$  is L, I, V, M, A or P;

$X_5$  is any amino acid;

$X_6$  is any amino acid;

$X_7$  is L, I, V, M, A, F, Y or W;

20  $X_8$  is C, T or S;

$X_9$  is R, K or H;

$X_{10}$  is any amino acid;

$X_{11}$  is any amino acid;

$X_{12}$  is L, I, V, M, A or P;

25  $X_{13}$  is any amino acid;

$X_{14}$  is any amino acid;

$X_{15}$  is any amino acid;

$X_{16}$  is L, I, V, M, A, P, G, C, T or S;

30  $[X_i]_n$  is a sequence of  $n$  amino acids wherein  $n$  is from 1 to 50 amino acids and wherein the sequence  $X_i$  may comprise the same or different amino acids selected from any amino acid residue;

(ii) comprises a SOCS box in its C-terminal region having the amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X]_n X_{17} X_{18} X_{19} X_{20}$   
 $X_{21} X_{22} X_{23} [X]_a X_{24} X_{25} X_{26} X_{27} X_{28}$  (SEQ ID NO: 51)

5

wherein:  $X_1$  is L, I, V, M, A or P;

$X_2$  is any amino acid residue;

$X_3$  is P, T or S;

$X_4$  is L, I, V, M, A or P;

10  $X_5$  is any amino acid;

$X_6$  is any amino acid;

$X_7$  is L, I, V, M, A, F, Y or W;

$X_8$  is C, T or S;

$X_9$  is R, K or H;

15  $X_{10}$  is any amino acid;

$X_{11}$  is any amino acid;

$X_{12}$  is L, I, V, M, A or P;

$X_{13}$  is any amino acid;

$X_{14}$  is any amino acid;

20  $X_{15}$  is any amino acid;

$X_{16}$  is L, I, V, M, A, P, G, C, T or S;

$[X]_n$  is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence  $X_i$  may comprise the same or different amino acids selected from any amino acid residue;

25  $X_{17}$  is L, I, V, M, A or P;

$X_{18}$  is any amino acid;

$X_{19}$  is any amino acid;

$X_{20}$  L, I, V, M, A or P;

$X_{21}$  is P;

30  $X_{22}$  is L, I, V, M, A, P or G;

$X_{23}$  is P or N;

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention provides a new family of modulators of signal transduction. As the initial members of this family suppressed cytokine signalling, the family is referred to as the 5 "suppressors of cytokine signalling" family of "SOCS". The SOCS family is defined by the presence of a C-terminal domain referred to as a "SOCS box". Different classes of SOCS molecules are defined by a motif generally but not exclusively located N-terminal to the SOCS box and which is involved by protein:molecule interaction such as protein:DNA or protein:protein interaction. Particularly preferred motifs are selected from an SH2 domain, WD-10 40 repeats and ankyrin repeats.

WD-40 repeats were originally recognised in the  $\beta$ -subunit of G-proteins. WD-40 repeats appear to form a  $\beta$ -propeller-like structure and may be involved in protein-protein interactions. Ankyrin repeats were originally recognised in the cytoskeletal protein ankyrin.

15

Members of the SOCS family may be identified by any number of means. For example, SOCS1 to SOCS3 were identified by their ability to suppress cytokine-mediated signal transduction and, hence, were identified based on activity. SOCS4 to SOCS15 were identified as nucleotide sequences exhibiting similarity at the level of the SOCS box.

20

The SOCS box is a conserved motif located in the C-terminal region of the SOCS molecule. In accordance with the present invention, the amino acid sequence of the SOCS box is:

25 
$$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_j]_n X_{17} X_{18} X_{19} X_{20} X_{21} X_{22} X_{23} [X_j]_n X_{24} X_{25} X_{26} X_{27} X_{28} \text{ (SEQ ID NO: 51)}$$

wherein:  $X_1$  is L, I, V, M, A or P;

$X_2$  is any amino acid residue;

$X_3$  is P, T or S;

30  $X_4$  is L, I, V, M, A or P;

$X_5$  is any amino acid;

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mouse SOCS-10 characterised by mb14d12, mb40f06, mg89b11, mq89e12, mp03g12 and vh53c11;

5 human SOCS-11 characterised by zt24h06 and zr43b02;

human SOCS-13 characterised by EST59161;

mouse SOCS-13 characterised by ma39a09, me60c05, mi78g05, mk10c11, mo48g12, mp94a01, vb57c07 and vh07c11; and

10 human SOCS-14 characterised by mi75e03, vd29h11 and vd53g07; or a derivative or homologue of the above ESTs characterised by a nucleic acid molecule being capable of hybridizing to any of the listed ESTs under low stringency conditions at 42°C.

15 In another embodiment, the nucleotide sequence encodes the following amino acid sequence:

X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> X<sub>4</sub> X<sub>5</sub> X<sub>6</sub> X<sub>7</sub> X<sub>8</sub> X<sub>9</sub> X<sub>10</sub> X<sub>11</sub> X<sub>12</sub> X<sub>13</sub> X<sub>14</sub> X<sub>15</sub> X<sub>16</sub> [X<sub>i</sub>]<sub>a</sub> X<sub>17</sub> X<sub>18</sub> X<sub>19</sub> X<sub>20</sub>  
X<sub>21</sub> X<sub>22</sub> X<sub>23</sub> [X<sub>j</sub>]<sub>a</sub> X<sub>24</sub> X<sub>25</sub> X<sub>26</sub> X<sub>27</sub> X<sub>28</sub> (SEQ ID NO:51)

20 wherein: X<sub>1</sub> is L, I, V, M, A or P;

X<sub>2</sub> is any amino acid residue;

X<sub>3</sub> is P, T or S;

X<sub>4</sub> is L, I, V, M, A or P;

25 X<sub>5</sub> is any amino acid;

X<sub>6</sub> is any amino acid;

X<sub>7</sub> is L, I, V, M, A, F, Y or W;

X<sub>8</sub> is C, T or S;

X<sub>9</sub> is R, K or H;

30 X<sub>10</sub> is any amino acid;

X<sub>11</sub> is any amino acid;

Still another embodiment of the present invention contemplates an isolated polypeptide or a derivative, homologue, analogue or mimetic thereof comprising a SOCS box in its C-terminal region.

5 Preferably the polypeptide further comprises a protein:molecule interacting domain such as a protein:DNA or protein:protein interacting domain. Preferably, this domain is located N-terminal of the SOCS box. It is particularly preferred for the protein:molecule interacting domain to be at least one of an SH2 domain, WD-40 repeats and/or ankyrin repeats.

10 Preferably, the signal transduction is mediated by a cytokine selected from EPO, TPO, G-CSF, GM-CSF, IL-3, IL-2, IL-4, IL-7, IL-13, IL-6, LIF, IL-12, IFN $\gamma$ , TNF $\alpha$ , IL-1 and/or M-CSF. Preferred cytokines are IL-6, LIF, OSM, IFN- $\gamma$  or thrombopoietin.

More preferably, the protein comprises a SOCS box having the amino acid sequence:

15

X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> X<sub>4</sub> X<sub>5</sub> X<sub>6</sub> X<sub>7</sub> X<sub>8</sub> X<sub>9</sub> X<sub>10</sub> X<sub>11</sub> X<sub>12</sub> X<sub>13</sub> X<sub>14</sub> X<sub>15</sub> X<sub>16</sub> [X]<sub>n</sub> X<sub>17</sub> X<sub>18</sub> X<sub>19</sub> X<sub>20</sub>  
 X<sub>21</sub> X<sub>22</sub> X<sub>23</sub> [X]<sub>n</sub> X<sub>24</sub> X<sub>25</sub> X<sub>26</sub> X<sub>27</sub> X<sub>28</sub> (SEQ ID NO:51)

wherein: X<sub>1</sub> is L, I, V, M, A or P;

20 X<sub>2</sub> is any amino acid residue;

X<sub>3</sub> is P, T or S;

X<sub>4</sub> is L, I, V, M, A or P;

X<sub>5</sub> is any amino acid;

X<sub>6</sub> is any amino acid;

25 X<sub>7</sub> is L, I, V, M, A, F, Y or W;

X<sub>8</sub> is C, T or S;

X<sub>9</sub> is R, K or H;

X<sub>10</sub> is any amino acid;

X<sub>11</sub> is any amino acid;

30 X<sub>12</sub> is L, I, V, M, A or P;

X<sub>13</sub> is any amino acid;